



PHARMACOVIGILANCE - POST MARKETING SURVEILLANCE NEWS

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Editor's Note

We wish to thank all our numerous stakeholders who have been working tirelessly with the National Pharmacovigilance Centre (NPC) to ensure the safe use of medicines in Nigeria. The NPC is committed to sending out quarterly newsletter to its stakeholders. The objectives of the Newsletter are to disseminate information on Pharmacovigilance activities nationally and globally, to educate stakeholders on medicine safety issues, to promote rational use of drugs and to promote spontaneous reporting. This second quarter newsletter focuses on Antibiotic Resistance and Pharmacovigilance. We encourage Health care Professionals and other stakeholders to continue to report all adverse drug reactions. Your valued comments and acknowledgement of receipt of this issue through our email addresses (nafdac_npc@yahoo.com; pharmacovigilance@nafdac.gov.ng) would be most appreciated.

Have a most blessed 2014!

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ANTIBIOTIC RESISTANCE AND PHARMACOVIGILANCE

Antibiotic resistance is a global problem with enormous public health significance; it threatens the developments made so far in the area of disease and infection control. The Centre for Disease Control (CDC) estimates that in the United States alone, more than two million people are sickened every year with antibiotic-resistant infections, with at least 23,000 dying as a result. Although most of these infections happen in the general community, the majority of deaths related to antibiotic resistance happen in healthcare settings such as the hospitals and nursing homes¹. Antimicrobial resistance (AMR) is resistance of a microorganism to an antimicrobial medicine to which it was originally sensitive². A resistant organism is able to withstand the therapeutic effects of an antimicrobial medicine resulting in a persistent infection/disease with complicated or limited treatment options (associated with higher costs), increased risk of transmission to others and worse treatment outcomes.

A growing number of pathogens are increasingly developing resistance to the antimicrobial agents used to treat infections. Various kinds of pathogenic bacteria, fungi, protozoa and viruses have developed resistance to their respective target antimicrobial agents. Some specific resistant organisms of public health significance include vancomycin-resistant *Staphylococcus aureus*, Vancomycin-resistant Enterococci (VRE), extensively drug-resistant *Mycobacterium tuberculosis*, (XDR TB) Carbapenem-resistant Enterobacteriaceae, Methicillin-resistant *Staphylococcus aureus* (MRSA). MRSA has become a major public health problem worldwide and recent reports indicate that the prevalence of hospital-associated MRSA (based on the detection of the *mecA* gene) in health care institutions in Nigeria may vary from 1.5% to 20%.³ Cases of fluoroquinolone-resistant *Neisseria meningitidis*⁴, gonorrhoea resistant to cephalosporin, (the last effective oral antibiotic used to treat the disease)⁵ and completely drug resistant TB have also been reported.

Nigeria is not without her share of epidemics of infections that were made worse by antibiotic resistance, such as the cholera outbreak of 1995 caused by bacteria that was resistant to chloramphenicol, spectinomycin, sulfonamides, and

trimethoprim. In addition, there have also been reports from different parts of the country on observed trends in the prevalence of resistance among enteric organisms, such as *Escherichia coli* and *Shigella* to multiple drugs including trimethoprim-sulphamethoxazole, ampicillin, tetracycline and chloramphenicol.⁶ A recent study conducted in Nigeria also highlighted a most alarming situation of highly diverse antibiotics resistance rates against most antibiotics ranging from 9.1 to 33.0%.⁷ currently, the Nigeria public health system is burdened with drug resistant problems such as drug resistant malaria, and multiple-drug resistant tuberculosis (MDR-TB).

Consequence of AMR to Pharmacovigilance

One major burden of antimicrobial resistance is that it compromises the use of previously effective treatments for infections. The clinician is faced with limited treatment options and may even completely run out of options in cases where the organism is resistant to all antibiotics that could be used to treat the infection. In circumstances where some option of second or even third line antibiotics still exists and are used, the safety of the patient may be further displaced; being that these drugs are often associated with a higher frequency of more serious adverse effects and worse treatment outcomes. This was elucidated in the write up on antituberculosis drugs in the first quarter 2014 newsletter, where it was indicated that most of the adverse events reported to the National Pharmacovigilance Centre (NPC) were on second line antituberculosis drugs. The first line drugs had events such gastrointestinal disorders, skin and subcutaneous tissue disorders, while the second line drugs in addition had more serious events such as psychosis, depression, peripheral neuropathy. Moreover the second and third line antibiotics are usually more expensive. Hence, patients' access to health care is also limited.

The pace of development of new antimicrobial agents especially ones with new mechanisms of action is not commensurate with the rate at which resistance is spreading. In 2008, a study of antibiotic development involving small firms as well as large pharmaceutical companies revealed that only 15 of 167 antibiotics under development had a new mechanism of action with the potential to meet the challenge of multi-drug resistance, however, most of the antibiotics

where still in the early stages of development⁸. This infers that in the near future, there may not be effective antibiotics with which to treat patients with serious infections.

Emergence and proliferation of resistance

The emergence of resistant microorganisms is fundamentally a natural phenomenon that occurs in the face of antibiotic use (be it in health care facilities, community and on the farm). A microorganism may be intrinsically resistant to one or more antibiotics. However, particularly bothersome is the acquisition of new resistance. An organism may develop new resistance through a process of random mutation where the presence of the antibiotic creates a selective pressure for the emergence of resistant strains. Antimicrobial resistance further proliferates aided by the ease at which microorganisms are able to transfer genetic material among them. Thus resistant strains may confer this ability to formerly susceptible organisms.⁹ These processes infer that the two major factors responsible for the persistence of antimicrobial resistance are the extent of antibiotic use and the prevalence of resistant genes. The human trend of misuse of antimicrobial agents is a major contributor to the emergence and proliferation of microbial resistance. Thus, regulating antibiotic use may play a role in reducing both pathogenic and non-pathogenic bacteria that may act as reservoir of resistant genes.

Surveillance

Although the problem of antibiotic resistance is not new and the WHO over the years has been advocating for concerted global, national and local efforts to contain it, the response has been insufficient. To further reframe the activities to be taken by the Member States, the WHO introduced a policy package to combat antimicrobial resistance on World Health Day of 2011. This policy has several components that border on parameters such as governments' commitment to a comprehensive national plan against antimicrobial resistance, strengthening surveillance and laboratory capacity, uninterrupted access to essential medicines of assured quality, promotion of rational use of antimicrobials etc¹⁰. The surveillance of antimicrobial resistant organisms is an essential tool needed to track changes in microbial populations,

ensure the early detection of resistant strains of public health importance, and for the prompt notification and investigation of outbreaks¹¹.

Also essential is the surveillance of antimicrobial use. Surveillance of antimicrobial use tracks how and why antimicrobials are being used and misused by patients and healthcare providers. Two important parameters here are prescription and consumption behaviour. These are expressed in practices such as prescribing antibiotics when they are not needed, patients not completing course of prescribed medicines and the purchase of antibiotics over the counter (OTC)/self-medication. Lack of quality-assured medicines at affordable prices and unauthorized vending of medicines also affects the consumption behaviour of patients. These create ideal conditions for the selection of resistant organisms. Monitoring the prescription and consumption of antibiotics will provide insights and tools needed to inform therapy decisions, to assess the public health consequences of antimicrobial misuse, and to evaluate the impact of resistance containment interventions¹².

The WHO also emphasizes the critical role of microbiological laboratories in the global strategy for containment of antimicrobial resistance. By implication, this strategy discourages the prescription of antibiotics without first conducting necessary tests. The choice of antibiotic use by the clinician should be guided by proper and adequate microbiological tests and should be in accordance with the recommended prescription guidelines. Excluding the role of the laboratory also infers that antibiotic resistance will often only be detected by therapeutic failure.

Conclusion

In our communities today, it is not uncommon to hear someone say “my body has stopped responding to so and so medicine(s)”, further enquiry will inform that the medicine in question is very often an antimicrobial agent. The problem is not necessarily unresponsive bodies but rather cases of pathogenic organisms that have become resistant to the antimicrobial agents. There is therefore need for correct/ responsible prescription and use of antibiotics, and also the

implementation of recommended surveillance strategies. The surveillance of antibiotic use and resistance in the country will help to mitigate paucity of information about current trends in antimicrobial resistance, hence inform about the true nature/ extent of the problem in our clime and guide in prevention strategies. Therapeutic failure should not be the determining factor for detecting resistance.

AMR REPORTS FROM THE NPC DATABASE

Reports on confirmed cases of AMR necessitating the use of second line medicines received by the NPC since 2004 were all due to MDR-TB. A total number of 183 ADR reports due to second line TB drugs were received within the reporting interval of 2004 to 2014. Other than these, the NPC has not received any explicit reports of AMR. Thus a search of the database based on the criteria of therapeutic failure was made and it generated 26 reports. Twenty of the reports were on antiretroviral drugs and the other five on antibiotics and one on antimalaria (see table 1 and 2 below)

As earlier mentioned in the literature review, therapeutic failure should not be the index for detecting antibiotic resistance as often is the case in our healthcare settings. Moreover therapeutic failure may result from other factors as well. In one of our earlier newsletters with focus on Spurious Substandard Falsified Falsely Labelled Counterfeit medicinal products (SSFFC), we had used the same criteria of therapeutic failure as the index for suspect SSFFC.

The paucity of data on this issue does not mean that we have been excused from the problem but rather that we are blind to the nature and extent of the problem in our country and hence cannot take adequate measures to curtail it.

Therapeutic failure with antiretroviral therapy

The NPC recorded a total of 20 individual case safety reports (ICSR) received on antiretroviral therapy that resulted in therapeutic failure

ANTIRETROVIRAL THERAPY	NO. OF REPORTS	INDICATION
Zidovudine/Lamivudine/Nevirapine	8	HIV
Nevirapine/Tenofovir/Lamivudine	7	HIV
Nevirapine/Tenofovir/Emtricitabine	1	HIV
Efavirenz/Zidovudine/Lamivudine	1	HIV
Efavirenz/Nevirapine/Zidovudine	1	HIV
Zidovudine/Lamivudine	1	HIV
Nevirapine/Tenofovir	1	HIV

Therapeutic failure with antibiotic and antimalarial use

Five individual case safety reports received on antibiotics use and one ICSR on antimalarial use also resulted in therapeutic failure.

DRUGS	INDICATION
Ceftriaxone(3)	Gangrene, fever, pyogenic meningitis
Levofloxacin	Infection
Ampicillin/clavulanate	Upper respiratory tract infection
Arthemether/benflumelol	Malaria

Source: Generated from the NPC database

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